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EFFECT OF DIFFERENT EXCIPIENTS ON THE RELEASE OF NORETHISTERON ACETATE FROM CHITOSAN-SODIUM ALGINATE POLYMERIC IMPLANTS

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Key words:

Biodegradable polymeric implant, Norethisteron Acetate, Chitosan, Sodium Alginate, SEM, DSC

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ABSTRACT: Biodegradable polymeric implant offers a novel approach for sustained drug delivery that provides an option to the patient of avoiding surgical retrieval of implant post-use. Chitosan, a biodegradable polymer extracted from the hard outer skeleton of shellfish, is used nowadays in many pharmaceutical applications (ophthalmic, nasal, sublingual, buccal, periodontal, gastrointestinal, colon-specific, vaginal, transdermal drug delivery and mucosal-vaccine). The main objective of the study was to prepare and evaluate an implantable system of Norethisteron Acetate with chitosan-sodium alginate. Norethisteron Acetate plays an important role in the long term treatment of abnormal uterine bleeding, amenorrhea, endometriosis and as contraceptive. Drug loaded Chitosan- Na Alginate implants were prepared in the ratios of 50:50, 60:40 and 70:30. As the 60:40 chitosan-sodium alginate ratio showed maximum sustained effect (8 days) it was further tested for sustained release potential with different excipients namely, Stearic Acid, Glyceryl Monostearte, Cety Alcohol and Dextrose. Implants with Glyceryl Monostearte sustained the release of drug the most (23 days). Effects of excipients were also observed on drug loading efficiency. Morphology of implant surfaces was observed with SEM both before and after drug release studies. Differential Scanning Calorimetry of drug loaded implants was also performed. The release kinetics of drug was evaluated by fitting the data in different kinetic models namely, Zero order, First order, Higuchi and Korsmeyer-Peppas. Implants were mostly found to follow Korsmeyer peppas model which indicate diffusion-controlled release from the where drug leaves the matrix through pores and channels formed by the entry of dissolution medium.

INTRODUCTION: Traditional drug delivery system has been characterized by immediate release and repeated dosing of the drug which might lead to the risk of dose fluctuation, this arises the need of a formulation with control release that maintain a near-constant or uniform blood level [1]. The development of Sustained release dosage forms is more likely to succeed commercially such as implants providing controlled, local release of active substances are of interest in different medical applications, assuming that they provide the desired efficacy and safety [2].

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By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients [1]. Polymeric drug delivery systems are an attractive alternative to control the release of drug substances to obtain defined blood level over a specified time [3]. Implantable drug delivery system can be classified into major categories: biodegradable or nonbiodegradable implants [4].

The process of biodegradation of a polymer implant begins with the polymer chains being broken into smaller fragments by hydrolysis. The molecular weight of the implant decreases first. Thereafter the mechanical strength of the implant decreases allowing subsequent mechanical fragmentation and absorption of the implant to begin. Actual mass loss of the implant occurs then

through the release of soluble degradation products, phagocytosis by macrophages and histiocytes, intracellular degradation and finally, metabolic elimination through the citric acid (Krebs) cycle to carbon dioxide and water, which are expelled from the body via respiration and urine. There is a danger of adverse tissue reaction if the rate of implant degradation produces more debris particles than the tissue is able to tolerate. This risk is greatest when the gross geometry of the implant is rapidly lost [5].

The most important advantage of biodegradable polymeric implant is the disappearance of implanted foreign materials from the body as a result of their biodegradation [6]. For incorporation of Norethisteron Acetate for better control of drug release, number of excipients is now used. Thus, more recent implants usually contain the drug in a rate controlling systems. These systems are available in a variety of sizes and shapes [7]. The basic goal of this therapy is to achieve a steady state blood level that is therapeutically effective and non toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal [8].

MATERIALS AND METHODS:

All the chemicals and reagents used in this study were of analytical grade. Norethisteron Acetate was obtained as a gift from Renata Limited, Bangladesh. Purified Chitosan were purchased from Haihang Industry Co., Ltd. China. Sodium Alginate, Stearic Acid, Glyceryl Monostearate (GMS), Cetyl Alcohol and Dextrose were purchased from Loba Chemie Pvt. Ltd, Mumbai. Acetonitrile was purchased from Fischer Chemical, New Jersey (NJ). Suitable storage conditions were maintained to store the working chemicals and reagents.

Preparation of implant:

Biodegradable implants of Norethisteron acetate were prepared by the use of two biodegradable polymers Chitosan and Sodium Alginate. Implants prepared using 25mg drug with different excipients with polymer ratio 60:40. The excipients used in different formulations are shown in **Table 1**. Preparation of implants using 100 ml of 1% acetic acid solution to dissolve 4.167g of chitosan. The solution was stirred until no large chunks remained and then blended until homogenous. 100ml of distilled water used to dissolve 4.167g of Na Alginate. The solution was stirred until no large chunks remained and added to the blended chitosan solution. Drug Norethisteron acetate was then dispersed to the Chitosan and Sodium Alginate solution. After being mixing with ultrasonic, the mixture was poured into petridish. Then they were allowed to set by placing in a refrigerator -32ºC for 1 day [9]. After 1 day, implants were cut into 1 cm width and 1 cm length square shape by NT cutter. Then implants were placed into a crosslinking solution of methanol containing 1% GA and 0.1 ml conc. HCl for hardening [10].

The contact time with crosslinking agent was 30 min for different formulations. Then they were washed with methanol and distilled water respectively. After hardening they were allowed to place it in aseptic cabinate for air drying for few minute. Formulations varied with respect to Chitosan-Sodium Alginate polymer ratios.

TABLE 1: EXCIPIENTS USED IN DIFFERENT FORMULATIONS

Name of Formulation	Drug	Used excipients
F1	Norethisteron Acetate	-
F2	Norethisteron Acetate	Stearic Acetate
F3	Norethisteron Acetate	Glyceryl Monostearate
F4	Norethisteron Acetate	Cetyl Alcohol
F5	Norethisteron Acetate	Dextrose

Characterization of Implants:

Photographic imaging:

The kinetics of drug release is greatly dependent on the morphological characters of implants [11]. Photographs of drug loaded implants are represented in **Fig. 1** were taken using Samsung Galaxy Duos, 12.0 Mega Pixel Camera.

Measurement of implant thickness:

The thickness of the implants was measured by picking three samples of implants for a particular formulation and exposure time, and measuring their thickness with slide calipers. The average thickness of implants hardened with Glutaraldehyde is shown in **Table 2.**

Weight variation of implants:

Weight variation of implants was checked by weighing three implants of a particular formulation [12]. The average weight of implants hardened with Glutaraldehyde is shown in **Table 2**.

FIG.1: PHOTOGRAPHIC IMAGE OF NORETHISTERON ACETATE IMPLANT

TABLE 2: THICKNESS & WEIGHT VARIATION OF NORETHISTERON ACETATE LOADED IMPLANTS WITH DIFFERENT EXCIPIENTS

Sl. no.	Formulation	Thickness of implant (mm) ± S.D.	Weight of implants (mg) ± S.D.
1	F1	2.76±0.041	221±0.81
2	F2	2.64±0.021	231±0.65
3	F3	2.55±0.045	235±0.045
4	F4	2.21±0.027	227±0.051
5	F5	2.35±0.034	243±0.067

Scanning electron microscope (SEM):

The internal morphology of the samples was evaluated by a SEM Philips XL30, (Netherlands). The implants were initially spread on a carbon tape glued to an aluminum stub and coated with Au using a Sputter Coater under vacuum in a closed chamber. The Au layer was coated to make the implant surface conductive to electrons in the SEM. The implants were then observed under SEM in varying magnifications and micrographs recorded.

Differential scanning calorimetry (DSC):

The DSC measurement was performed on a DSC-60 (SHIMADZU) differential scanning calorimetry with a thermal analyzer (TA-60WS). Precise amounts of 7.5 mg of Norethisteron Acetate + Chitosan + Na Alginate sample were placed in a sealed aluminium pan, before heating under nitrogen flow (300 ml/min) at a scanning rate 10ºC min-1 from 30°C to 400°C. An empty aluminum pan was used as reference (Dhaka, Bangladesh).

Determination of drug content (loading dose):

The amount of drug that was actually loaded in implants during fabrication process was determined by spectrophotometric analysis. A weighed Norethisteron Acetate implant was crushed by a porcelain mortar and pestle. Then it was dissolved in 2ml Acetic Acid by vigorous ultrasonication. Then 2ml of Acetronitrile, 4ml hot buffer and 2ml Acetic Acid added for precipitating the polymer and extracting the drug in solvent. That means the total volume of Acetic Acid, Acetronitrile and phosphate buffer (pH7.4) ratio is 4:2:4. Then it was centrifuged at 4000 RPM for 15 minute to separate the solid material. Clear supernatant was withdrawn and it was analyzed at 240nm (λmax of Norethisteron Acetate) in UV spectrophotometer. Norethisteron Acetate concentration was calculated from the standard curve.

The % loading efficiency (LE) of implants was determined with the formula:

$$\%LE = (LD/AD) \times 100$$

Where,

LD is the amount of loaded drug in the implant and

AD is the amount of added drug in the formulation [13].

FIG.2: IMAGE OF CRUSHED IMPLANT

***In-vitro* dissolution studies:**

The in-vitro release of Norethisteron Acetate from implants was carried out in static conditions at 37°C. The weighed implants (at least 3 implants) from each formulation and exposure time were kept in rubber capped glass vessels containing 100 ml of Phosphate Buffer, pH 7.4. 5 ml of the release medium was collected at predetermined time intervals and replaced with 5 ml of fresh buffer to maintain the sink condition. The withdrawn samples were then analyzed for determining the percentage of release of drugs by UV spectrophotometer (UV-1700 Pharma Spec, SHIMADZU) at 240 nm (λ_{max} of Norethisteron Acetate in Phosphate Buffer, pH 7.4), after subsequent dilution of the samples. All data were used in statistical analysis for the determination of mean, standard deviation and release kinetics.

Statistical analysis:

Results were expressed as mean ± S.D. Statistical analysis was performed by linear regression analysis. Coefficients of determination (R^2) were utilized for comparison. *In-vitro* release studies were performed under the same conditions for each implant system. The means and standard deviations were calculated at each time interval. The means were graphed for each release profile with the standard deviations included as error bars. Linear regression was performed on cumulative drug release as a function of time and also on fitted curves to different kinetic models.

RESULTS AND DISCUSSION:

Observation through Scanning Electron Microscope (SEM):

The SEM micrograph of Glyceryl Monostearate (as excipient) loaded Norethisteron Acetate polymeric implant surface before and after drug release are represented in **Fig.3, 4** respectively. They display a 50 times magnified polymeric implant surface. The more hydrophobic the polymer, the smoother the surface [14]. The rough implant surface as observed in the SEM micrograph of **Fig. 3** which is indicative of the hydrophilic nature of the polymer matrix. This hydrophilic nature of chitosan and sodium alginate is supported by Dutta *et al*. [15] and Aslani *et al*. [16], respectively. **Fig.4** displays the implant surface after drug release. The pores on the surface as seen in the figure are created by the entry of the dissolution media while drug release continues.

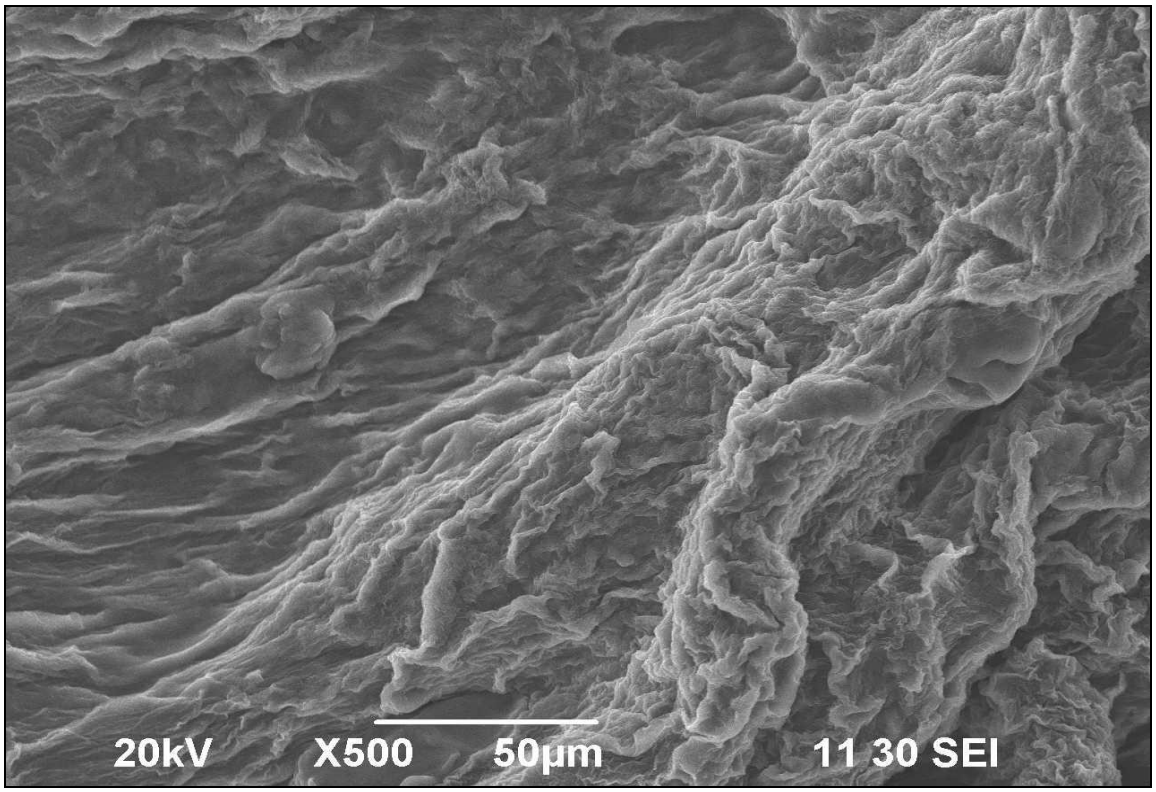

FIG.3: SEM MICROGRAPH OF NORETHISTERON ACETATE BIODEGRADABLE POLYMERIC IMPLANT INCORPORATED WITH GLYCERYL MONOSTEARATE SURFACE BEFORE DRUG RELEASE

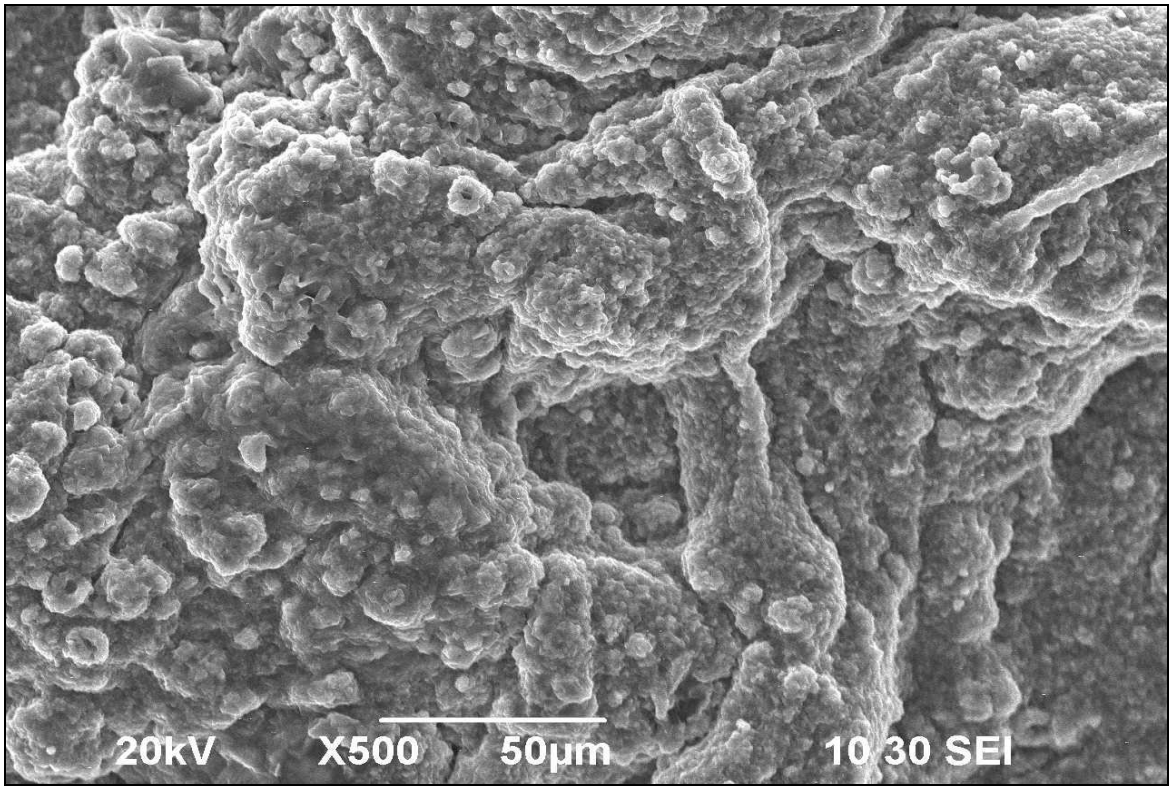

FIG. 4: SEM MICROGRAPH OF NOETHISTERON ACETATE BIODEGRADABLE POLYMERIC IMPLANT INCORPORATED WITH GLYCERYL MONOSTEARATE SURFACE AFTER DRUG RELEASE

Differential Scanning Calorimetry (DSC) of Drug and Polymer:

The DSC scans of pure Norethisteron Acetate incorporated in Chitosan-Sodium alginate mixture was also performed in **Fig. 6**. Endothermic peak found at onset temperature 197.02ºC and endset temperature 246.50ºC. These figure 5 exhibits Norethisteron Acetate incorporated in Chitosan-Sodium Alginate mixture having broad endothermic peak at 230.59ºC. **Fig. 5** represents the characteristic endothermic peak of pure Norethisteron Acetate is at 162.49°C. However, a little difference in endothermic peak of Norethisteron Acetate has been noted. When Norethisteron Acetate incorporated in Chitosan-Sodium Alginate mixture, the characteristic endothermic peak of Norethisteron Acetate at 162.49ºC has shifted to 197.02ºC which can be attributed to the presence of polymer [17]. The presence of the polymer in the formulation probably raised the melting point of Norethisteron Acetate causing the shift of endothermic peak to 197.02°C.

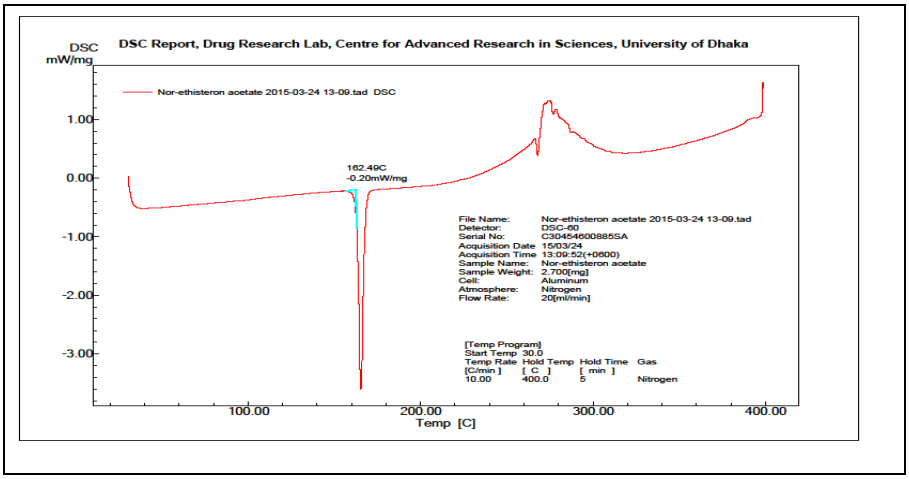

FIG.5: DSC THERMOGRAPH OF PURE NORETHISTERON ACETATE

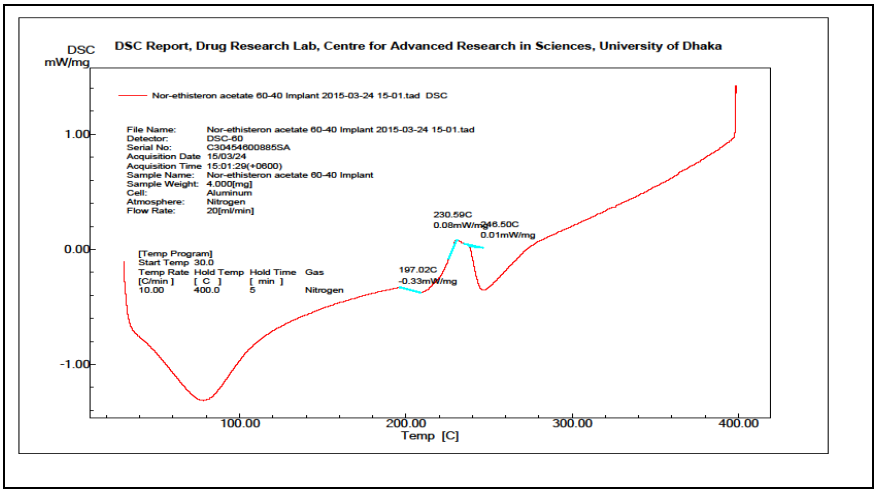

FIG. 6: DSC THERMOGRAPH OF NORETHISTERON ACETATE INCORPORATED IN CHITOSAN-SODIUM ALGINATE POLYMERIC IMPLANT

Effect of Excipients Loading Efficiency of Gelatin- Sodium Alginate Polymeric Implants:

The effect of incorporating different excipients on drug loading efficiency of Norethisteron Acetate was studied for 25mg drug load. The excipient load was the same as the drug load. The changes in the loading efficiency were probably caused by the respective excipients. The data for different excipients with 25mg load of Norethisteron Acetate are represented in **Table 3**. Loading efficiency was found in the range between 48.92% to 75.56% from different formulations. The highest loading efficiency was found with Dextrose (75.56%) and the lowest with GMS (48.92%).

The loading efficiency was found to decrease in the following sequence:

Dextrose> Stearic Acid > Cetyl Alcohol > Drug only > GMS

Dextrose is soluble in water and thereby increased loading efficiency [18]. Stearic Acid is practically insoluble in water [19] and thereby decreases the passage for drug which may result in high drug loading efficiency. Stearic Acid has a lower acid value: 200-21215, indicating its hydrophobic nature [20]. Stearic Acid and Mg Stearate are practically insoluble in water [21] for which they may dissolve in DMSO and decrease the passage for hydrophilic drug which may result in increased drug loading efficiency. Cetyl Alcohol has been used in matrix-controlled drug delivery system for its hydrophobic property [22]. Glyceryl Monostearate has a HLB value of 3.8, which indicates its hydrophobic nature. It is also practically insoluble in water. Therefore, it probably decreases the dispersibility of the drug [23]. Therefore, it increases drug loading efficiency. It is found to decrease drug loading as compared to the formulation without excipient. This is probably due to its effect in increasing the affinity between the solvent and non solvent.

TABLE 3: EFFECTS OF EXCIPIENTS ON NORETHISTERON ACETATE LOADING EFFICIENCY (%) OF CHITOSAN- SODIUM ALGINATE POLYMERIC IMPLANTS

Excipients	Loading Efficiency (%)
Drug only (F1)	62.36
Stearic Acid (F2)	72.44
Glyceryl Monostearate (F3)	48.92 (minimum)
Cetyl Alcohol (F4)	64.32
Dextrose (F5)	75.56 (maximum)

***In-vitro* Drug Release Studies:**

A biodegradable polymeric implant can function by releasing a drug in the correct amount of strength over a period of time following one or a combination of mechanisms viz., erosion of the matrix, diffusion through the matrix or combination of both diffusion and erosion mechanisms either enzymatically or non-enzymatically to produce biocompatible or nontoxic by-products [24]. The drug release rate from a polymeric matrix depends on interactions between the active ingredients and polymer [25]. In the literature, plenty of theoretical or empirical release models are described [26-27]. Zero order, First order kinetics, Higuchi and Korsmeyer-Peppas models have been chosen to describe the Norethisteron Acetate release from Chitosan-Sodium Alginate biodegradable polymeric implants. The zero order rate equation describes the

systems where the drug release rate is independent of its concentration. The first order equation describes the release from the system where release rate is concentration dependent. Higuchi describes the release of drugs from insoluble matrix as a square root of time dependent process based on the Fickian diffusion [28].

The Korsmeyer-Peppas equation describes the mode of release of drugs from swellable matrices [29]. Assuming perfect sink conditions, rapid surface equilibrium between the polymer and water, symmetric devices, and uniformly dispersed drug in the dry sample [19]. The *in vitro* release pattern of drug with various excipient-loaded implants are presented in **Table 4 and Fig.7**. Norethisteron Acetate release from implants with various types of excipients for 30 minute glutaldehyde exposure time was continued for 23 days is shown in **Fig. 7**. The release gradually decreased and remained constant for 23 days. Formulation F3 containing Glyceryl Monosterate gave more controlled release of Norethisteron Acetate as time progressed.

As Glyceryl Monosterate is hydrophobic in nature, it decreases the hydrophilicity of biodegradable implant [23], which decreases the release of Norethisteron Acetate from the formulation. This is expected from any hydrophobic excipients as they would prevent the drug from diffusing from the polymer matrix into the aqueous solution.

TABLE 4: OVERVIEW OF CALCULATED TIME DESCRIBING THE IN VITRO NORETHISTERON ACETATE RELEASE FROM CHITOSAN-NA ALGINATE POLYMERIC IMPLANT

Excipients	Calculated time (days) for drug release
Drug only (F1)	8
Stearic Acid (F2)	17
Glyceryl Monostearate (F3)	23
Cetyl Alcohol (F4)	12
Dextrose (F5)	10

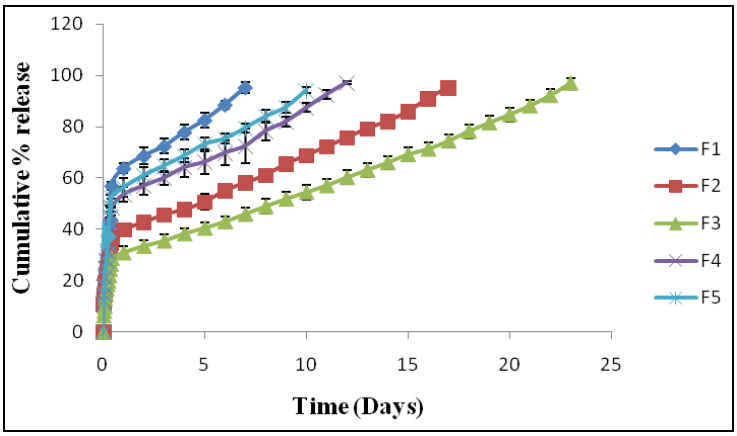

FIG.7: AVERAGE NORETHISTERON ACETATE RELEASE PATTERN FROM IMPLANTS WITH FOUR DIFFERENT EXCIPIENTS (STEARIC ACID, GMS, CETYL ALCOHOL, DEXTROSE) WITH DRUG ONLY

Different kinetic models were utilized to analyze the possible drug release mechanism. The release from most of the implants with excipients best fitted to korsmeyerpeppas kinetic model and regression analysis was performed on the fitted curves. As can be seen, the zero order fits for Chitosan-Sodium Alginate implants with different excipients showed the highest R^2 values among all the models (R^2 values in **Tables 5**). In the present study almost as good correlations were obtained with korsmeyer-peppas model as well. According to these models **Fig. 11**, Norethisteron Acetate release from the implants is diffusion controlled with the drug leaving the matrix through pores and channels formed by the entry of dissolution medium [30]. SEM micrograph also supports that Norethisteron Acetate leaves the matrix through pores and channels is represented in **Fig. 4**. The roughness and the caves observed on the surface could provide physical evidence of diffusion release mechanism [31].

The Korsmeyer-Peppas release rate constant for the implants was found to be within 0.45-0.89 ($0.45<n<0.89$) which indicates the major mechanism of drug release being nonfickian diffusion [32] which appears to indicate a coupling of the diffusion and erosion mechanism [33].

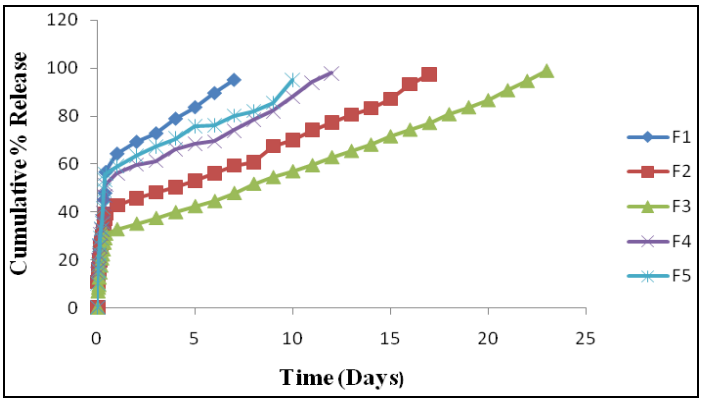

FIG.8: ZERO ORDER PLOT OF NORETHISTERON ACETATE RELEASE FROM IMPLANTS WITH DIFFERENT EXCIPIENT

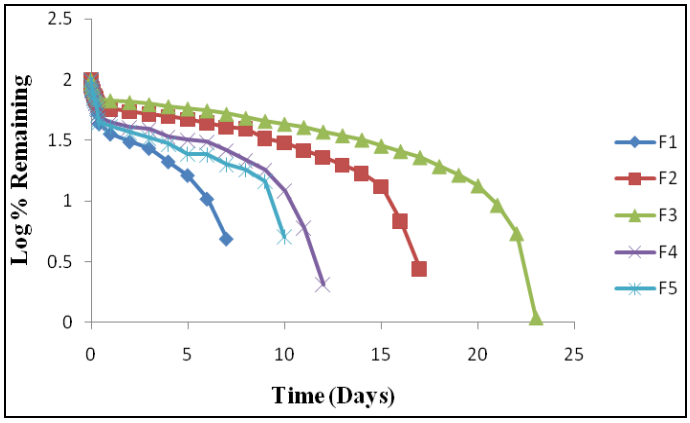

FIG.9: FIRST ORDER PLOT OF NORETHISTERON ACETATE RELEASE FROM IMPLANTS WITH DIFFERENT EXCIPIENTS

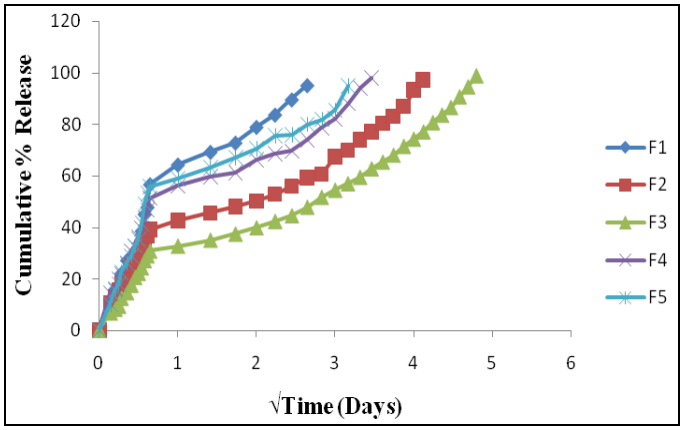

FIG. 10: HIGUCHI PLOT OF NORETHISTERON ACETATE RELEASE FROM IMPLANTS WITH DIFFERENT EXCIPIENTS

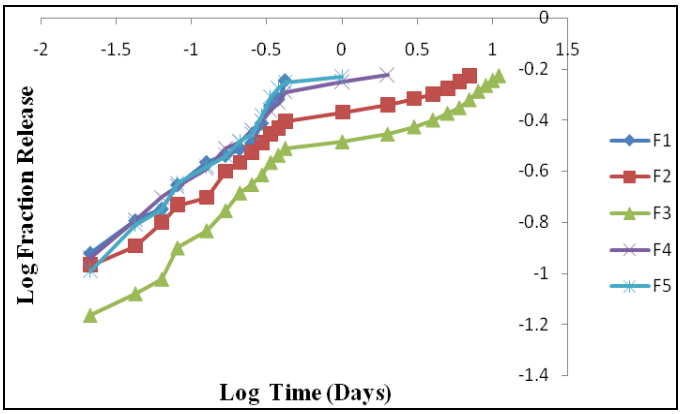

FIG. 11: KORSMEYER-PEPPAS PLOT OF NORETHISTERON ACETATE RELEASE FROM IMPLANTS WITH DIFFERENT EXCIPIENTS

TABLE 5: FITTING COMPARISON OF EQUATION OF HIGUCHI, KORSMEYER-PEPPAS, FIRST ORDER AND ZERO ORDER FOR DESCRIBING NORETHISTERON ACETATE RELEASE FROM IMPLANTS WITH DIFFERENT EXCIPIENTS

Formulations	Kinetic model							
	Zero order		First order		Higuchi		Korsmeyer peppas	
	m value	R^2	m value	R^2	m value	R^2	m value	R^2
F1	11.02	0.757	-0.15	0.938	32.03	0.901	0.484	0.965
F2	4.343	0.897	-0.057	0.869	18.09	0.948	0.275	0.913
F3	3.472	0.946	-0.046	0.798	16.55	0.965	0.307	0.925
F4	6.006	0.805	-0.090	0.869	21.81	0.908	0.394	0.943
F5	6.947	0.723	-0.088	0.883	23.78	0.860	0.501	0.961

CONCLUSION: Use of Norethisteron Acetate, which is an attractive treatment option for the secondary amenorrhea, endometriosis, and abnormal uterine bleeding due to hormonal imbalance and for contraception. Therefore, this drug appears to be particularly suitable for targeted and controlled release drug delivery system. Considerable efforts are being made for sustaining its release for prolonged use and research works have already been reported on entrapping the drug, utilizing nanoparticle technology and thermoplastic biodegradable polymeric drug delivery devices. The present study revealed that Norethisteron Acetate could be entrapped into Chitisan-Sodium alginate implants with high drug loading efficiency (48.92-75.56%) and also provide sustained drug release for a period of 10-23 days. Therefore, this work can be taken further to explore its potential in this indication.

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